

LLOREDA & CIA. S. A.
ABOGADOS

BOGOTA - COLOMBIA
OFICINA FUNDADA EN 1941
APARTADO AEREO 12304
TEL: 57-1-3264270 57-1-6069700
FAX: 57-1-3264271 57-1-6069701
CABLES: LLOREDA
CALLE 72 No. 5-83 5º. PISO
www.lloredacamacho.com
jllico@lloredacamacho.com

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-128643- -00003-0000

Fecha: 2007-08-08 16:18:42 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 538 PETICION Folios: 2

Re: P1.-ASTRAZENECA AB.-Solicitud de Patente de Invención en
Fase Nacional PCT para "NOVEDOSO COMPUESTO DE
IMIDAZOPIRIDINA II CON EFECTO TERAPÉUTICO".-Clase
C07D 471/04-Expediente número 05-128.643.-

1. Me refiero a mi memorial de 24 de Abril de 2006.
2. De conformidad con lo dispuesto en el Artículo 5.2.12 de la Circular Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial número **573** de 28 de Febrero de 2007, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.
3. Me permito recordar a usted, que tal como se informó en el Petitorio de la invención, la presente solicitud corresponde a Capítulo I.
4. Anexo me permito acompañar recibo número 07-62.675, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

Señor Superintendente,


ALICIA LLOREDA RICAURTE

T.P. 53.215



US006313137B1

(12) **United States Patent**
Amin et al.

(10) Patent No.: **US 6,313,137 B1**
(45) Date of Patent: **Nov. 6, 2001**

(54) **IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION**

0228006 7/1987 (EP)
0308917 3/1989 (EP)

(75) Inventors: **Kosrat Amin; Mikael Dahlström**, both of Mölndal; **Peter Nordberg**, Sövedalen; **Ingemar Starke**, Göteborg, all of (SE)

(73) Assignee: **AstraZeneca AB**, Sodertälje (SE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/319,973**

(22) PCT Filed: **Apr. 23, 1999**

(86) PCT No.: **PCT/SE99/00663**

§ 371 Date: **Jun. 14, 1999**

§ 102(e) Date: **Jun. 14, 1999**

(87) PCT Pub. No.: **WO99/55706**

PCT Pub. Date: **Nov. 4, 1999**

(30) **Foreign Application Priority Data**

Apr. 29, 1998 (SE) 9801526

(51) Int. Cl.⁷ **A61K 31/435; C07D 471/04**

(52) U.S. Cl. **514/300; 546/121**

(58) Field of Search **546/121; 514/300**

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,450,164 5/1984 Bristol et al. 546/121
4,725,601 2/1988 Ueda et al. 514/300

FOREIGN PATENT DOCUMENTS

0033094 8/1981 (EP)
0204285 12/1986 (EP)

OTHER PUBLICATIONS

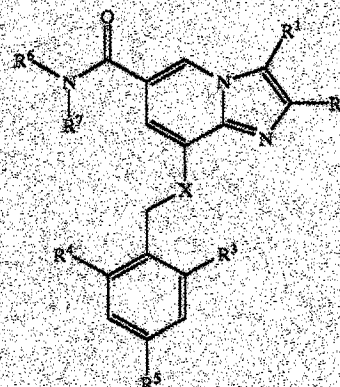
Kaminski, et al., J. Med. Chem. 28, 876-892 (1985).
Kaminski, et al., J. Med. Chem. 30, 2031-2046 (1987).
Kaminski, et al., J. Med. Chem. 30, 2047-2051 (1987).
Kaminski, et al., J. Med. Chem. 32, 1686-1700 (1989).
Kaminski, et al., J. Med. Chem. 34, 533-541 (1991).

Primary Examiner—Bernard Dentz

(74) Attorney, Agent, or Firm—White & Case LLP

(57) **ABSTRACT**

The present invention relates to imidazo pyridine derivatives of the formula (I), in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with a carboxamide group in 6-position, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases.



22 Claims, No Drawings

IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION

This application is a 371 of PCT/SE99/00663 filed Apr 23, 1999.

TECHNICAL FIELD

The present invention relates to novel compounds, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above. The invention also relates to new intermediates for in the preparation of the novel compounds.

BACKGROUND ART

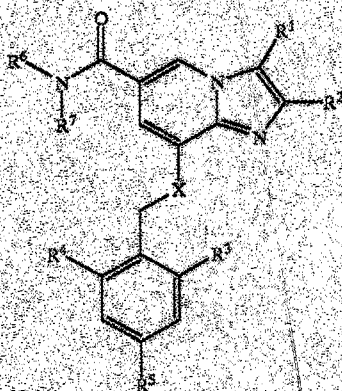
Substituted imidazo[1,2-a]pyridines, useful in the treatment of peptic ulcer diseases, are known in the art, e.g. from EP-B-0033094 and U.S. Pat. No. 4,450,164 (Schering Corporation); from EP-B-0204285 and U.S. Pat. No. 4,725,601 (Fujisawa Pharmaceutical Co.); and from publications by J. J. Kaminski et al. in the Journal of Medical Chemistry (vol. 28, 876-892, 1985; vol. 30, 2031-2046, 1987; vol. 30, 2047-2051, 1987; vol. 32, 1686-1700, 1989; and vol. 34, 533-541, 1991).

For a review of the pharmacology of the gastric acid pump (the H⁺, K⁺-ATPase), see Sachs et al. (1995) Annu. Rev. Pharmacol. Toxicol. 35: 277-305.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the Formula I, which are imidazo pyridine derivatives in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with a carboxamide group in 6-position are particularly effective as inhibitors of the gastrointestinal H⁺, K⁺-ATPase and thereby as inhibitors of gastric acid secretion.

In one aspect, the invention thus relates to compounds of the general Formula I



or a pharmaceutically acceptable salt thereof, wherein

R¹ is

- (a) H,
- (b) CH₃, or
- (c) CH₂OH,

R² is

- (a) CH₃,
- (b) CH₂CH₃,

R³ is

- (a) H
- (b) C₁-C₆ alkyl,
- (c) hydroxylated C₁-C₆ alkyl,
- (d) halogen

R⁴ is

- (a) H,
- (b) C₁-C₆ alkyl,
- (c) hydroxylated C₁-C₆ alkyl, or
- (d) halogen;

R⁵ is

- (a) H, or
- (b) halogen;

R⁶, R⁷ are the same or different

- (a) H,
- (b) C₁-C₆ alkyl;
- (c) hydroxylated C₁-C₆ alkyl
- (d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl

X is

- (a) NH, or
- (b) O.

As used herein, the term "C₁-C₆ alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C₁-C₆ alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

The term "halogen" includes fluoro, chloro, bromo and iodo.

Both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the invention. It should be understood that all the diastereomeric forms possible (pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention. Also included in the invention are derivatives of the compounds of the Formula I which have the biological function of the compounds of the Formula I, such as prodrugs.

It will also be appreciated by those skilled in the art, although derivatives of compounds of formula I may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolized in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds of formula I are included within the scope of the invention.

Depending on the process conditions the end products of the Formula I are obtained either in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

Acid addition salts of the new compounds may in a manner known per se be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

In the preparation of acid addition salts, preferably such acids are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids such as hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulphonc acids, such as formic acid, acetic acid,

9

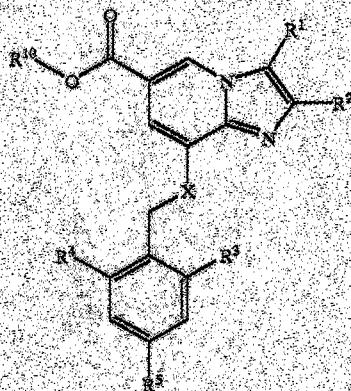


wherein R^6 and R^7 are as defined in Formula I to the corresponding amide of the Formula I wherein R^1 is H or CH_3 and X is NH. The reaction can be carried out by heating the reactants in the neat amino compound or in an inert solvent under standard conditions.

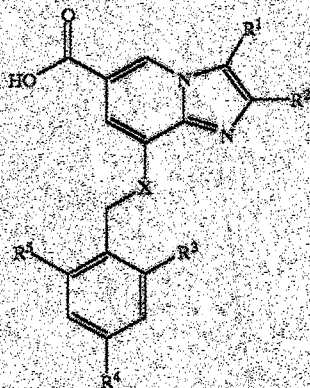
Process C

Process C for manufacture of compounds with the general Formula I comprises the following steps:

a) Treating compounds of Formula XVII



wherein R^1 , R^2 , R^3 , R^4 , R^5 , and X are as defined in Formula I and R^{10} is an alkyl group such as methyl, ethyl, etc., with acid or base under standard conditions can hydrolyzed them to the corresponding carboxylic acid compounds of Formula XVIII



b) Compounds of the Formula XVIII wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined in Formula I can be reacted with amino compounds of Formula III in the presence of a coupling reagent to the corresponding amide compounds of the Formula I. The reaction can be carried out in an inert solvent under standard conditions.

Medical Use

In a further aspect, the invention relates to compounds of the formula I for use in therapy, in particular for use against gastrointestinal inflammatory diseases. The invention also provides the use of a compound of the formula I in the manufacture of a medicament for the inhibition of gastric

10

acid secretion, or for the treatment of gastrointestinal inflammatory diseases.

The compounds according to the invention may thus be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance.

Pharmaceutical Formulations

In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient.

The compounds of the invention can also be used in formulations together with other active ingredients, e.g. antibiotics such as amoxicillin.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains at least one compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1-95% by weight of the preparation, preferably between 0.1-20% by weight in preparations for parenteral use and preferably between 0.1 and 50% by weight in preparations for oral administration.

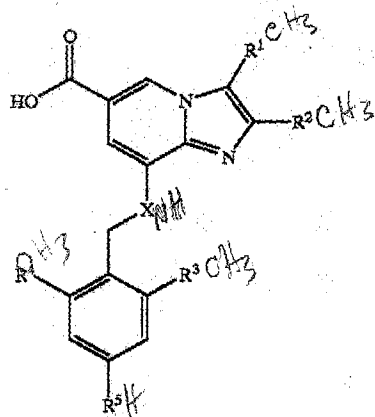
In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Hard gelatin capsules may contain granules of the active compound. Hard gelatin capsules may also contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatin rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro

13

(e) a compound of the formula XVIII



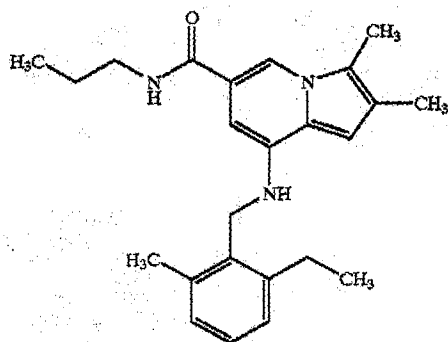
wherein R¹, R², R³, R⁴, R⁵, and X are as defined for Formula I.

EXAMPLES

PREPARATION OF COMPOUNDS OF THE INVENTION

Example 1.1

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-propyl-imidazo[1,2-a]pyridine-6-carboxamide



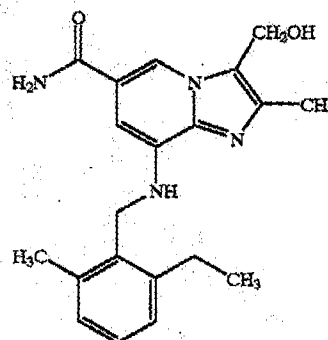
Ethyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate (0.12 g, 0.33 mmol), propylamine (1.0 g, 17 mmol) and a cat. amount of sodium cyanide were refluxed in methanol (20 ml) for 24 h. An additional amount of propylamine (1.0 g, 17 mmol) was added and the reaction mixture was refluxed for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using diethyl ether as eluent. Crystallization from diethyl ether gave 0.053 g (42%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 1.0 (t, 3H), 1.2 (t, 3H), 1.65-1.75 (m, 2H), 2.3 (s, 3H), 2.35 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 3.4-3.5 (m, 2H), 4.35 (d, 2H), 4.9 (bs, 1H), 6.35 (s, 1H), 7.0-7.2 (m, 4H), 7.85 (s, 1H).

14

Example 1.2

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide

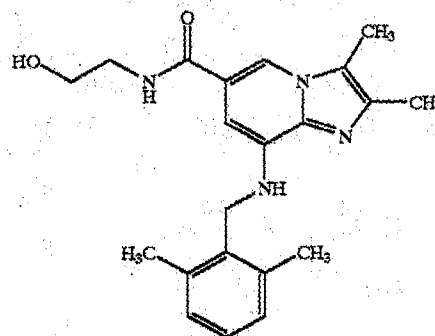


Ethyl 6-(aminocarbonyl)-8-(2-ethyl-6-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine-3-carboxylate (280 mg, 0.71 mmol) and lithium borohydride (16 mg, 0.71 mmol) were added to tetrahydrofuran (10 ml) and the reaction mixture was refluxed for 70 min. Additional amounts of lithium borohydride (16 mg) and methanol (45 mg, 1.42 mmol) were added and the mixture was refluxed for 80 min. Additional amounts of lithium borohydride (16 mg) and methanol (22 mg, 71 mmol) were added and the mixture was refluxed for 4 h. The reaction mixture was allowed to reach R.T. and water (1 ml) and methanol (5 ml) and was stirred for 40 min. at R.T. The solvents were evaporated under reduced pressure and the residue was added to water and was stirred for 80 min. The crystals were filtered off and washed with water, ethyl acetate/ethanol and diethyl ether to give the desired product (115 mg, 46%).

¹H-NMR (300 MHz, DMSO-d₆): δ 1.15 (t, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.35 (d, 2H), 4.75 (d, 2H), 4.85 (t, 1H), 5.1 (t, 1H), 6.8 (s, 1H), 7.1-7.25 (m, 3H), 7.4 (bs, 1H), 8.05 (bs, 1H), 8.3 (s, 1H)

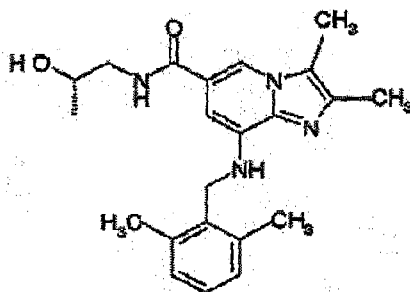
Example 1.3

Synthesis of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide



Methyl 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate (0.12 g, 0.33 mmol), ethanolamine (0.2 g, 3.3 mmol) and sodium cyanide (10 mg, 0.2 mmol) were refluxed in dimethoxyethane (2 ml) for 20 h. The solvent was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using methylene chloride:methanol (92:8) as eluent gave the product which was washed with diethyl ether to give 103 mg (79%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 2.3 (s, 6H), 2.35 (s, 6H), 3.5-3.6 (m, 2H), 3.75-3.8 (m, 2H), 4.3 (d, 2H), 4.95 (t, 1H), 6.4 (s, 1H), 6.85 (t, 1H), 7.0-7.2 (m, 3H), 7.75 (s, 1H)



La reivindicación 3, se trata del proceso para obtener dicho compuesto; la reivindicación 5, menciona una formulación farmacéutica conteniendo el compuesto de fórmula (I); la reivindicación 6 reclama el intermediario del proceso de fabricación de fórmula (III).

IPC: A61K31/437, A61P1/04. C07D471/04.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

La reivindicación 4, se caracteriza por un uso.

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria: 26/06/2003.

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D1	US 6,313,137	Imidazo pyridine derivatives Which inhibit gastric acid secretion	Noviembre/6/2001

D1 US 6,313,137 (folios: 68-72)

4. Análisis de patentabilidad (artículo 14 D486)

4.1 Novedad (artículo 16 D486)

Respecto a la solicitud en estudio:

La reivindicación 1, reclama: "Un compuesto de fórmula (I), o una sal aceptable del mismo.

La reivindicación 3, menciona: "Un proceso para obtener el compuesto de fórmula (I)".

La reivindicación 6, dice: "Un compuesto de fórmula (III)